

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/00	A2	(11) International Publication Number: WO 00/16761 (43) International Publication Date: 30 March 2000 (30.03.00)
<p>(21) International Application Number: PCT/US99/19888</p> <p>(22) International Filing Date: 3 September 1999 (03.09.99)</p> <p>(30) Priority Data: 60/101,067 18 September 1998 (18.09.98) US</p> <p>(71) Applicant (for all designated States except US): ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): MAY, Jesse, A. [US/US]; 4132 Hildring Drive East, Fort Worth, TX 76109 (US). DEAN, Thomas, R. [US/US]; 101 Meadow View Court, Weatherford, TX 76087 (US). SHARIF, Najam, A. [GB/US]; 7 Courtney Court, Arlington, TX 76015 (US).</p> <p>(74) Agents: YEAGER, Sally, S. et al.; R & D Counsel Q-148, Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, TX 76134-2099 (US).</p>		<p>(81) Designated States: AU, BR, CA, CN, JP, KR, MX, TR, US, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>
<p>(54) Title: SEROTONERGIC 5HT₂ AGONISTS FOR TREATING GLAUCOMA</p> <p>(57) Abstract</p> <p>Compounds with 5HT₂ receptor agonist activity useful for treating glaucoma, including lowering intraocular pressure. Compositions and methods for their use are also disclosed.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

SEROTONERGIC 5HT₂ AGONISTS FOR TREATING GLAUCOMA

5 The present invention is directed to the use of compounds with serotonergic 5HT₂ agonist activity (Compound) to treat glaucoma, which includes lowering intraocular pressure.

10 Background of the Invention

Serotonin (5-hydroxytryptamine; 5HT) is an endogenous biogenic amine with a well defined neurotransmitter function in many tissues of the body including the eye [Zifa and Fillion, *Pharmacol. Rev.*, **44**, 401 (1992); Hoyer et al., *Pharmacol. Rev.*, **46**, 157 (1994);
15 Tobin et al., *J. Neurosci.*, **8**, 3713 (1988)].

5HT can interact with at least seven major 5HT receptors (5HT₁ - 5HT₇) and additional subtypes within these families to initiate intracellular biochemical events such as stimulation of second messengers (e.g. cAMP, inositol trisphosphate) eventually leading to
20 the final biological response, for example, tissue contraction or hormone release, etc. [Hoyer et al., *supra*; Martin et al., *Trends Pharmacol. Sci.*, **19**, 2 (1998)]. Receptor subtypes within the 5HT₁ family are negatively coupled to adenylyl cyclase (AC) and cause inhibition of cAMP production, while 5HT₄, 5HT₆, and 5HT₇ receptors are positively coupled to AC and thus stimulate cAMP production when activated by 5HT [Martin et al., *supra*]. The 5HT₃
25 receptor is unique in that it couples to an ion channel which gates sodium, potassium, and calcium [Hoyer et al., *supra*].

The receptors in the 5HT₂ family are positively coupled to phospholipase C (PLC) and thus generate inositol phosphates and mobilize intracellular calcium when activated by 5HT.
30 The 5HT₂ receptor classification consists of the 5HT_{2A}, 5HT_{2B}, and 5HT_{2C} receptor subtypes, all of which have highly homologous amino acid sequences. The receptor previously referred to as 5HT_{1C} in an earlier nomenclature (prior to about 1990), has been reclassified as the 5HT_{2C} receptor because of its greater similarity with other PLC coupled receptors of the

5HT₂ family, based on molecular cloning and its pharmacological characteristics (Hoyer, et al, 1994).

Serotonergic nerves innervate the eye [Tobin et al., *J. Neurosci.*, **8**, 3713 (1988)] and
5 5HT has been found in the aqueous humor of human eyes [Martin et al., *Ophthalmol.*, **95**,
1221 (1988)]. In addition, receptor binding sites for [³H]5HT have been demonstrated and
pharmacologically characterized in the iris-ciliary body (ICB) of rabbits [Mallorga and
Sugrue, *Curr. Eye Res.*, **6**, 527 (1987) and Chidlow et al., *Invest. Ophthalmol. Vis. Sci.*, **36**,
2238 (1995)]. These 5HT binding sites have been shown to be functionally coupled to
10 second messenger generation in rabbits [Tobin and Osborne, *J. Neurochem.*, **53**, 686 (1989)
and Tobin et al., *J. Neurosci.*, *supra*]. In the human ICB these binding sites are characterized
as 5HT_{1A} and 5HT₂ receptors [Barnet and Osborne, *Exp. Eye Res.*, **57**, 209 (1993)]. In
addition, the presence of mRNAs for 5HT_{1A} and 5HT₇ receptors in the rabbit ICB have been
reported [Chidlow et al., *Invest. Ophthalmol. Vis. Sci.*, *supra* and Osborne and Chidlow,
15 *Ophthalmologica*, **210**, 308 (1996)]. The precise functions of these receptors in the eye are
unknown.

5HT or 5-carboxamidotryptamine (5-CT) topically applied to the rabbit eye raise
intraocular pressure (IOP) [Meyer-Bothling et al., *Invest. Ophthalmol. Vis. Sci.*, **34**, 3035
20 (1993)]. By contrast, another group has shown that topically applied 5HT decreased IOP in
the rabbit; however, when 5HT was administered to the rabbit intracamerally it resulted in an
increase in IOP and caused breakdown of the blood-aqueous barrier [Krootila et al., *J. Ocular
Pharmacol.*, **3**, 279 (1987)]. In addition, the 5HT uptake inhibitor, fluoxetine (Prozac®), also
raises IOP in human subjects upon oral administration [Costagliola et al., *Br. J. Ophthalmol.*,
25 **80**, 678 (1996)] and may cause glaucoma [Ahmad *Ann. Pharmacother.*, **25**, 436 (1992)].
However, the 5HT receptor subtype(s) involved in the IOP-elevating effects of 5HT, 5-CT
and fluoxetine are unknown.

Studies conducted in rabbits with 8-hydroxy DPAT and MKC-242 (5HT_{1A} agonists)
30 have shown these compounds lower IOP [Osborne and Chidlow *Ophthalmologica*, **210**, 308
(1996), and EP 0771563-A2]. In addition, 5-methylurapidil (5HT_{1A} agonist) lowered IOP in
glaucomatous monkeys [Wang et al., *Curr. Eye Res.*, **16**, 679 (1997)]. Both MKC-242 and 5-

methylnurapidil are relatively potent α_1 receptor antagonists (α_1 antagonists are known to lower IOP in rabbits, monkeys, and man). The mechanism of action for lowering IOP by 5-methylnurapidil has been attributed to its α_1 antagonist activity and not its 5HT_{1A} agonist activity [Wang et al., *Invest. Ophthalmol. Vis. Sci.*, 39(Suppl), 2236 (1998)]. U.S. Patent No. 5,693,654, discloses 5HT₁-like (now designated 5HT_{1D}) receptor agonists, such as sumatriptan, for lowering IOP. WO92/20338 discloses certain 5HT_{1A} antagonists for the treatment of glaucoma.

Methysergide (5HT₂ antagonist, but with other activities) lowered IOP in rabbits [Krootila et al., *Exp. Eye Res.*, *supra*]. Ketanserin (5HT_{2A/C} antagonist), also with significant α_1 antagonist activity, lowers IOP in rabbits and man [Chan et al., *J. Ocular Pharmacol.*, 1, 137 (1985) and Costagliola et al., *Exp. Eye Res.*, 52, 507 (1991)]. Saproterate (5HT_{2A} antagonist) lowers IOP in rabbits and in man when dosed topically or orally [Mano et al., *Invest. Ophthalmol. Vis. Sci.*, 36(Suppl), 3322 (1995) and Takenaka et al., *Invest. Ophthalmol. Vis. Sci.*, 36(Suppl), 3390 (1995)]. EP 522226 and U.S. Patent No. 5,290,781 disclose the use of ketanserin and its derivatives for treating ocular hypertension. U.S. Patent Nos. 5,290,781 and 5,106,555 disclose the use of certain 5HT₂ antagonists for lowering IOP. U.S. Patent No. 5,652,272 discloses saproterate for reducing IOP. U.S. Patent No. 5,538,974 discloses ophthalmic compositions of certain 5HT₂ antagonists for lowering IOP. WO/9911619 discloses 5HT_{2A} antagonists which may be efficacious in treating glaucoma.

U.S. Patent No. 5,011,846 discloses certain 5HT₃ receptor antagonists for treating glaucoma.

WO 97/17345 discloses that particular compounds with 5HT₄ serotonergic receptor agonist or antagonist activity are useful for treating psychiatric, gastrointestinal, lower urinary, and cardiovascular disorders. The publication mentions the compounds may also be useful for glaucoma.

As evidenced by the previous discussion, it is not clear which serotonergic receptor activity is responsible for lowering IOP. Moreover, a number of these compounds are known

to have activity at non-serotonergic receptors which are known to be involved in lowering IOP.

Summary of the Invention

5

The present invention is directed to the use of compounds with 5HT₂ receptor agonist activity to treat glaucoma, which includes lowering intraocular pressure. Compositions of the compounds are contemplated for such uses.

10

Detailed Description Preferred Embodiments

Unexpectedly, it has been found that serotonergic compounds which possess agonist activity at 5HT₂ receptors effectively lower and control elevated IOP and are useful for treating glaucoma.

15

Specific compounds which exemplify the present invention include: 1) (R)-4-iodo-2,5 dimethoxy- α -methyl-benzeneethanamine [(R)-DOI], the prototypical selective 5HT₂ agonist which is not selective amongst the 5HT₂ receptor subtypes [Baxter et al., *Trends Pharmacol. Sci.*, **16**, 105 (1995)]; 2) α -methyl-serotonin, a potent 5HT₂ agonist with modest receptor subtype selectivity: 5HT_{2B}>5HT_{2C}>5HT_{2A} [Baxter, et al., *supra*]; 3) 5-methoxy- α -methyltryptamine, with a profile similar to that of α -methyl-serotonin [Nichols et al., *J. Med. Chem.*, **31**, 1406 (1998)]. The following references are not limiting, but rather exemplify Compounds useful according to the present invention and are incorporated herein by reference: U.S. Patent Nos. 5,861,425; 5,646,173; 5,578,612; 5,571,833; 5,545,644; 5,494,928; 4,659,706 and 4,487,773; published European Patent Specification No. 863,136; published International Patent Application Nos. WO98/56768; WO98/31354; WO98/30548; WO98/30546. Additionally, compounds disclosed in the following publications further exemplify Compounds useful according to the present invention and are also incorporated herein by reference: Parker et al, *J. Med. Chem.* **41**, 5148 (1998); Vangveravong et al, *J. Med. Chem.* **41**, 4995 (1998); Albertini et al, *Mutagenesis*, **13**, 397 (1998); Monte et al, *J. Med. Chem.* **40**, 2997 (1997); Bös et al., *Eur. J. Med. Chem.*, **32**, 253 (1997); Bös et al., *J. Med. Chem.*, **40**, 2762 (1997); Monte et al, *J. Med. Chem.* **39**, 2952 (1996); Glennon et al., *J. Med.*

30

Chem., 37, 1929 (1994); Macor et al, *Tetrahedron Lett.* 35, 45 (1994); Macor et al, *J. Med. Chem.* 35, 4503 (1992); Macor et al. *J. Med. Chem.*, 35, 3625 (1992); Glennon et al, *J. Med. Chem.* 35, 734 (1992); Seggel et al. *J. Med. Chem.* 33, 1032 (1990).

5 It is recognized that many of the aforementioned Compounds have asymmetric atoms, therefore all enantiomers and diastereomers are contemplated. Also contemplated are pharmaceutically acceptable salts as well as the free bases of the Compounds. The Compounds are administered to the eye (e.g., topically, intracamerally, or via an implant). The Compounds are preferably incorporated into topical ophthalmic formulations for delivery
10 to the eye. The Compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a Compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may
15 include an ophthalmologically acceptable surfactant to assist in dissolving the Compound. Furthermore, the ophthalmic solution may contain an agent to increase viscosity, such as, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan
20 and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-940, or the like, according to the published formulations for analogous
25 ophthalmic preparations; preservatives and tonicity agents can be incorporated.

The Compounds are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The Compounds will normally be contained in these formulations in an amount 0.01% to 5% by weight, but preferably in an amount of 0.25% to
30 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the routine discretion of a skilled clinician.

The Compounds can also be used in combination with other agents for treating glaucoma, such as, but not limited to, β -blockers, prostaglandins, carbonic anhydrase inhibitors, α_2 agonists and miotics. The Compounds can also be used with calcium channel blockers and antagonists for metabotropic and ionotropic glutamate receptors and/or
5 antagonists for their associated binding sites, such as, the polyamine and strychnine-insensitive glycine sites. These agents may be administered topically, but usually systemically.

A particularly preferred combination includes the use of a Compound with an α_2
10 adrenergic agent, such as, apraclonidine or brimonidine or their pharmaceutically acceptable salts.

Compounds useful in this invention can be identified using methodology well known to one skilled in the art. The selection is made first by using a 5HT₂ receptor binding assay,
15 an example of which is described below. Compounds of this invention possess high affinity for 5HT₂ receptors (IC₅₀ or K_i values of about 20nM or less and this affinity is higher than at other 5HT receptors). The second part of this selection is made based on the functional activity of the compound as described below. Compounds of this invention possess agonist EC₅₀ values of about 1 μ M or less. Antagonists are not contemplated in this invention.

Both of these methods are believed to be the best way to identify a compound that would be useful according to this invention; however, it is important to note that some compounds that are identified by these methods may not be as desirable as others as commercial products. One must take into account the nature of the compound in question in
25 terms of its structure, physical properties – e.g., solubility, lipophilicity, and chemical stability and its susceptibility to be metabolized to an inactive compound (or compounds) within the eye. The impact of these parameters is well known to one skilled in the art and can be determined using methods well known in the art.

30 In addition to the above discussion, certain 5HT₂ agonists such as DOI, its isomers, and related compounds are known to cause central nervous system (CNS) side effects in man

when dosed systemically. In the present invention it is believed that the Compounds can be dosed topically, at a low enough dose to lower and control IOP, but not cause unwanted CNS side effects which may be associated with some Compounds. Some Compounds are particularly desirable because their physical properties keep them from penetrating the CNS and causing side effects. Also, certain Compounds of this invention may cause local irritation and discomfort upon topical ocular administration that render them less desirable than other more comfortable compounds. This can be readily determined using methods well known in the art.

EXAMPLE 1

5HT₂ Receptor Binding Assay

In order to determine the relative affinities of serotonergic compounds at the 5HT₂ receptors, their ability to compete for the binding of the agonist radioligand [¹²⁵I]DOI to brain 5HT₂ receptors is determined as described below with minor modification of the methods of Johnson et al. (*Neuropharmacology*, 26, 1803 (1987)). Aliquots of post mortem rat or human cerebral cortex homogenates (400 µl) dispersed in 50 mM TrisHCl buffer (pH 7.4) are incubated with [¹²⁵I]DOI (80 pM final) in the absence or presence of methiothepin (10 µM final) to define total and non-specific binding, respectively, in a total volume of 0.5 ml. The assay mixture is incubated for 1 hr at 23°C in polypropylene tubes and the assays terminated by rapid vacuum filtration over Whatman GF/B glass fiber filters previously soaked in 0.3% polyethyleneimine using ice-cold buffer. Test compounds (at different concentrations) are substituted for methiothepin. Filter-bound radioactivity is determined by scintillation spectrometry on a beta counter. The data are analysed using a non-linear, iterative curve-fitting computer program (Bowen & Jerman, *Trends Pharmacol. Sci.*, 16, 413 (1995)) to determine the compound affinity parameter. The concentration of the compound needed to inhibit the [¹²⁵I]DOI binding by 50% of the maximum is termed the IC₅₀ or K_i value. Compounds are considered to possess high affinity for the 5HT₂ receptor if their IC₅₀ or K_i values are ≤50 nM.

5HT₂ Functional Assay: Phosphoinositide (PI) turnover assay

The relative agonist activity of serotonergic compounds at the 5HT₂ receptor can be determined in vitro using the ability of the compounds to stimulate the production of [3H]inositol phosphates in [3H]myo-inositol-labeled A7r5 rat vascular smooth muscle cells by their ability to activate the enzyme phospholipase C. These cells are grown in culture plates, maintained in a humidified atmosphere of 5% CO₂ and 95% air and fed semi-weekly with Dulbecco's modified Eagle medium (DMEM) containing 4.5 g/l glucose and supplemented with 2mM glutamine, 10 µg/ml gentamicin, and 10% fetal bovine serum. For the purpose of conducting the phosphoinositide (PI) turnover experiments, the A7r5 cells are cultured in 24-well plates as previously described (Griffin et al., *J. Pharmacol. Expt. Ther.*, **286**, 411 (1998)). Confluent cells are exposed for 24-30 hrs to 1.5 µCi [3H]-myo-inositol (18.3 Ci/mmol) in 0.5 ml of serum-free medium. Cells are then rinsed once with DMEM/F-12 containing 10 mM LiCl prior to incubation with the test agent (or solvent as the control) in 1.0 ml of the same medium for 1 hr at 37°C, after which the medium is aspirated and 1 ml of cold 0.1 M formic acid added to stop the reaction. The chromatographic separation of [3H]-inositol phosphates ([3H]-IPs) on an AG- 1-X8 column is performed as previously described (Griffin et al., *J. Pharmacol. Expt. Ther.*, **286**, 411 (1998)) with sequential washes with H₂O and 50 mM ammonium formate, followed by elution of the total [3H]-IPs fraction with 1.2 M ammonium formate containing 0.1 M formic acid. The eluate (4 ml) is collected, mixed with 15 ml scintillation fluid, and the total [3H]-IPs determined by scintillation counting on a beta-counter. Concentration-response data are analyzed by the sigmoidal fit function of the Origin Scientific Graphics software (Microcal Software, Northampton, MA) to determine agonist potency (EC₅₀ value) and efficacy (E_{max}). Serotonin (5HT) is used as a positive control (standard) agonist compound and the efficacy of test compounds is compared to that of 5HT (set at 100%). The concentration of the compound needed to stimulate the production of [3H]-IPs by 50% of the maximum response is termed the EC₅₀ value. Compounds are considered potent agonists if their EC₅₀ values in this functional assay are ≤ 1 µM and are considered full agonists if their efficacy is > 80% of that of 5HT.

The above procedures were used to generate the data shown in Table 1.

Table 1. 5HT₂ Receptor Binding and Functional Data for Representative Compounds.

Compound	IC ₅₀ , nM (SEM)	EC ₅₀ , nM (SEM)	Efficacy (E _{max} , %)
(R)-DOI	0.5 ± 0.2	277 ± 35	82
α-Methylserotonin	3.5 ± 0.9	189 ± 26	104
5-Methoxy-α-methyltryptamine	2.5 ± 0.9	286 ± 39	107
Serotonin	0.8 ± 0.2	338 ± 27	100

Acute IOP Response in Lasered (Hypertensive) Eyes of Conscious Cynomolgus Monkeys

Intraocular pressure (IOP) was determined with an Alcon Pneumatonometer after light corneal anesthesia with 0.1% proparacaine. Eyes were washed with saline after each measurement. After a baseline IOP measurement, test compound was instilled in one 30 µL aliquot to the right eyes only of nine cynomolgus monkeys. Vehicle was instilled in the right eyes of six additional animals. Subsequent IOP measurements were taken at 1, 3, and 6 hours.

The profile of the IOP response following topical administration for each of these Compounds is provided in Table 2.

Table 2. IOP Response for Representative Compounds

Example	Dose, µg	Baseline IOP (mmHg)	Percent IOP Reduction ± SEM		
			Hours after dose		
			1	3	6
(R)-DOI	100	31.9	11.0 ± 4.98	25.3 ± 2.97	34.4 ± 4.98
α-Methylserotonin	250	41.8	14.2 ± 4.39	25.8 ± 5.16	30.8 ± 7.72
5-Methoxy-α-methyltryptamine	300	38.1	21.6 ± 5.05	35.2 ± 6.12	33.4 ± 5.39
Serotonin	250	33.5	13.3 ± 5.31	18.0 ± 5.12	2.0 ± 7.39

The following topical ophthalmic formulations are useful according to the present invention administered 1-4 times per day according to the discretion of a skilled clinician.

EXAMPLE 2

Ingredients	Amount (wt %)
5HT ₂ Compound	0.01 – 2%
Hydroxypropyl methylcellulose	0.5%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

5

EXAMPLE 3

Ingredients	Amount (wt %)
5HT ₂ Compound	0.01 – 2%
Hydroxypropyl methylcellulose	0.5%
Cremophor EL	0.1%
Tromethamine, USP, AR	0.64%
Mannitol, USP	3.0%
Boric acid, USP	0.3%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 4

Ingredients	Amount (wt %)
5HT ₂ Compound	0.01 – 2%
Methyl cellulose	4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 5

Ingredients	Amount (wt %)
5HT ₂ Compound	0.01 – 2%
Hydroxypropyl- β -cyclodextrin	4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 6

Ingredients	Amount (wt %)
5HT ₂ Compound	0.01 – 2%
Xanthan gum	0.5-6.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 7

Ingredients	Amount (wt %)
5HT ₂ Compound	0.01 – 2%
Guar gum	0.4- 6.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

5

EXAMPLE 8

Ingredients	Amount (wt %)
5HT ₂ Compound	0.01 – 2%
Tyloxapol	0.2 – 4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

10

EXAMPLE 9

Ingredients	Amount (wt %)
5HT ₂ Compound	0.01 – 2%
White petrolatum and mineral oil and lanolin	Ointment consistency
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4

5

EXAMPLE 10

Ingredients	Amount (wt %)
5HT ₂ Compound	0.01 – 2%
Brimonidine	0.2%
Hydroxypropyl methylcellulose	0.5%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

We Claim:

1. A method for treating glaucoma which comprises administering to a person in need thereof, a composition comprising a pharmaceutically effective amount of a compound with
5 5HT₂ receptor agonist activity.

2. The method of Claim 1 wherein the 5HT₂ receptor agonist is present at a concentration of 0.01 weight percent to 5 weight percent.

10 3. The method of Claim 2 wherein the concentration is 0.25 weight percent to 2 weight percent.

4. The method of Claim 1 wherein the 5HT₂ receptor agonist is (R)-DOI, α -Methylserotonin, 5-Methoxy- α -methyltryptamine.
15

5. The method of Claim 1 wherein the composition additionally comprises another compound selected from the group consisting of β -blockers, prostaglandins, carbonic anhydrase inhibitors, α_2 agonists, and miotics.

20 6. The method of Claim 5 wherein the compound is an α_2 agonist.

7. The method of Claim 6 wherein the α_2 agonist is selected from the group consisting of apraclonidine and brimonidine.

25 8. A composition for treating glaucoma comprising a pharmaceutically effective amount of a compound with 5HT₂ receptor agonist activity.

9. The composition of Claim 8 wherein the 5HT₂ receptor agonists concentration is 0.01 weight percent to 5 weight percent.
30

10. The composition of Claim 9 wherein the concentration is 0.25 weight percent to 2 weight percent.

11. The composition of Claim 8 wherein the 5HT₂ receptor agonist is selected from the group consisting of (R)-DOI, α -Methylserotonin, 5-Methoxy- α -methyltryptamine.

12. The composition of Claim 8 wherein the composition additionally comprises another compound selected from the group consisting of β -blockers, prostaglandins, carbonic anhydrase inhibitors, α_2 agonists, and miotics.

13. The composition of Claim 12 wherein the compound is an α_2 agonist.

14. The composition of Claim 13 wherein the α_2 agonist is selected from the group consisting of apraclonidine and brimonidine.

BLANK PAGE